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Pensee T. Do
Patent Examiner
Tel: 1-571-272-0819
Fax: 1-703-872-9306 571-273-8300

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06/19/2006

Qing Wang
95 Knickerbocker Road
Plainview, NY 11803
Tel/Fax: 1-516-390-9304
Email:qbwang888@yahoo.com

Dear Ms. Pensee T. Do,

Thank you for all your assistance in my patent application process. Please find attached my response to the latest non-final rejection. I apologize for the lack of clarity in my earlier submissions as my English was not quite good at the time and it was difficult for me to express my ideas in a clear way. In fact, my patent lawyer had to hire a translator to work with me on the first drafting of my patent. However, I believe that my English is much better at this point and that my ideas are able to be clearly expressed. Thus, I thank you for your patience and time in reviewing my patent application.

There are three parts in my Patent Argument (Application/Control Number: 10/723,923):

1. A general statement
2. What we learned from the previous art (Because I did not get the printed patents, so I have to use only the parts in given to me in the non-final rejection; I am sorry if it is any inconvenience for you to read.)
3. Conclusion of why my patent is still unique and non-obvious.

Sincerely,

Qing Wang Qing Wang

SIGNED AND ATTESTED TO MY PRESENCE THIS 20TH DAY OF JUNE 2006 AT PLAINVIEW, NEW YORK

JOSEPH LEAVY
Notary Public - State of New York
NO. 01LE6136860
Qualified in Nassau County
My Commission Expires 11/14/09

Patent Argument (Application/Control Number: 10/723,923)
(06/19/06)

Dear Ms. Do, Pensee T

After reading and learning carefully about the Patent law and the Articles you sent to me, I still believe that no one has been able to teach the method stated in my patent. Allow me to describe the patent in question:

1. General Statement

On my patent (Application Number 10/723.923), Detailed Description of Preferred Embodiments, "[0008] To prepare the beads used in the invention, a solution of N-succinimidyl S-acetylthioacetate ("SATA' hereafter) was prepared by admixing 2.0 mg of SATA with 0.5 mL of dimethyl formamide (DMF). SATA is used herein because it contains both a protecting group, i.e., an acetate moiety, for a free sulfhydryl group, and an N-hydroxysuccinimide moiety, which is a good leaving group."

Apart from DMF, there is no other buffer or other solution. That is to say, my method is performed with only DMF as the reaction intermediate.

In [0009], "This resulted in attachment of SATA to the beads, via an acylation reaction with the free primary amine group on the beads. The N-hydroxysuccinimide moiety is a leaving group, as noted, supra. If the beads are not be used immediately, the free sulfhydryl group remains protected."

The protected sulfhydryl group is very stable in the DMF. This kind of bead can be mass produced and sent out worldwide to support scientific research.

The claim 10 is based on the detailed descriptions of preferred embodiments [0008] and [0009]. In other words, without support of [0008] and [0009], claim 10 is too general to practice. The importance of my patent lies in the methods and results of my experiments over the general concept of the experiments. In overview of Claim 10 and Detailed Description of Preferred Embodiments together, I definitely think that there are major differences between my patent and the others in question. This is a new method: the special solvent, DMF, was used in my patent to enable a rapid reaction. The reaction also takes place in higher quantity than the others, producing stable beads that are far easier to manufacture for the support of scientific research.

2. What We Learn From the Previous Arts

Let me use the same way that I have evaluated my invention (by evaluating claims and experiments together) to view the previous arts. We cannot only learn what they claim in the general statements, we have to learn what they are teaching us to do in the experiment. They cannot simply state a concept, saying, "This method is the best way," without backing up with experimental results proving such. If they do so, they limit the progress of science in finding new and improved methods by only using general statements to prove their validity. For example, no matter what the following articles are claiming in their general teachings, you will find that their experiments are still being carried out in an aqueous intermediate—they have not achieved the non-aqueous

intermediate as I have. Without consensus in the general statements and the experimental results, these patents will slow the reaching of the best method or mislead the search for the best results quickly and economically.

Let see what Abrams (US 6,492,118) teaches us in EXAMPLES

Example 1
"Derivatization Of Polystyrene Microspheres With An Acrylamide-Functional Nucleic Acid
FIG. 1 depicts schematically one method for covalently bonding acrylamide functional nucleic acids to a polystyrene support. In Step 1, the formation of latent thiol groups on amino-functional polystyrene is illustrated. Approximately 10 .mu.L of amino-functional polystyrene microspheres (10% suspension) were dispersed in 80 .mu.l of phosphate buffer (50 mM, pH=7.5). The amino-functional polystyrene microspheres had a diameter of approximately 1 .mu.m and an amino group density of approximately 75 .mu.eq/g (Bang's Laboratories Inc., Fisher, Ind.). To the polystyrene microsphere suspension, 368 .mu.g of N-succinimidyl S-acetylthioipropionate (hereinafter "SATP"), (Pierce, Rockford, Ill.) in 10 .mu.l of dimethyl sulfoxide (hereinafter "DMSO") was slowly added. This mixture was gently shaken for approximately two (2) hours at ambient temperature. The microspheres were then washed three (3) times, each time with 100 .mu.l of phosphate buffer (50 mM, pH=7.5), by adding the phosphate buffer and mixing, centrifuging, and decanting the supernatant, to provide latent thiol microspheres after the final decanting step."

Example 2
Array Formation On An Aminoalkyl Glass Slide
A glass slide having a plurality of amine groups attached in a substantially uniform spatial pattern to a flat surface thereof (Part #S 4651, aminoalkyl silane coated slides, Sigma Chemical Co., St. Louis, Mo., 1999 catalog) was submerged for two (2) hours at ambient temperature in a solution of 15 mM SATP in 50 mM phosphate buffer pH 7.5, 10% DMSO. The glass slide was then washed three (3) times with 50 mM, pH 7.5 phosphate buffer by submerging the glass slide in phosphate buffer. A glass slide having a plurality of latent thiolated groups was formed.

Example 3
Array Formation on a Polystyrene Support
A polystyrene flat support having a plurality of amine groups attached in a substantially uniform spatial pattern to a flat surface thereof is submerged for two (2) hours at ambient temperature in a solution of 15 mM SATP in dimethyl sulfoxide-phosphate buffer. Then, the polystyrene flat support is washed three (3) times with 50 mM, pH=7.5 phosphate buffer, submerging the polystyrene flat support in phosphate buffer to provide a polystyrene flat support having a plurality of latent thiolated sites.

Example 10
Preparation Of Thin Gel Supports With Reduced BAC, Thioacetic Acid Method

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The following was added to a 15 ml tube: 100 mg BAC 1.0% 0.384 mmole 0.5 ml DMF 0.5 ml water After the BAC was dissolved, the following was added: 43.8 mg thioacetic acid 0.384 mmole After the incubation, the following was added: Final conc: 1.5 ml 40% stock acrylamide/bis solution 6.0% (844 mM) 2.0 ml 500 mM Tris-Glycine buffer pH 9.0 100 mM 5.0 ml water 10 ml total

Example 11
Comparison of BAC, AEMA, and reduced BAC Supports For Microarray Hybridization; Effect Of Buffer And Glycerol In Spotting Solutions

Example 12
Preparation of Acrylate Slides with 1-6% BAC Polymerization In Organic Solvent Without Comonomer

Acrylate slides were co-polymerized in BAC solutions containing concentrations of BAC ranging from 1% to 6%. A 1% BAC coated slide was made by mixing 3 ml of 10% BAC in DMF; 12 ml of DMF; 15 ml of water and 600 .mu.L of 25% APS; 100 .mu.L TEMED. After mixing, this solution was dispensed into a container with four acrylate slides; the solution was allowed to polymerize overnight at room temperature. A white homogenous gel-like material signaled the visible onset of polymerization. The BAC acrylate slides were then removed from the solution and rinsed in deionized water with gentle rubbing to remove the visible white film formed on the BAC acrylate slide.

Example 13
Preparation of Acrylate Slides with BAC-Comonomer-Polymerization in Organic Solvent A procedure similar to that in Example 7 was used to make slides with 2% BAC, with various amounts of P400mm. To make a slide with a coating of 2%/BAC-1% P400mm, four acrylate slides were immersed in a solution made by mixing: 3.6 ml of 10% BAC in DMF; 5.4 ml of DMF; 9 ml of water; 180 .mu.L of P400mm; 240 .mu.L of 25% APS; 40 .mu.L TEMED. After standing at room temperature, the appearance of the solution was noted. The BAC acrylate slides were then removed from the solution and rinsed in deionized water. In cases where a film was visible on the slides, gentle rubbing was used to remove the visible white film. The BAC acrylate slides were again washed in water, and then dried with a stream of nitrogen.

Example 14
Preparation of Acrylate Slides with BAC-Polymerization in Water
1% BAC in water coated slides were prepared as follows: 0.5 g of BAC was dissolved in 50 ml of deionized water at 70.degree. C. Acrylate slides were completely submerged in the heated BAC solution. 1.0 ml of 0.05% APS and 1.0 ml of 0.05% TEMED were added. The container was sealed and shaken for 1 minute. The polymerization reaction was complete within several minutes. A white precipitate of polyBAC formed. After removal of the macroscopic polyBAC particulate with water, the acrylate slides appeared coated with a homogeneous thin white film. This film was removed by gentle scrubbing under

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water. The resulting dried BAC acrylate slides appeared clear and transparent with no visible residue.

We see that in every experiment noted above, the purpose of using DMSO/DMF was to help SATP become more soluble in phosphate buffer (50 mM, pH=7.5). Thus, the reaction is still taking place in an aqueous solution, and DMSO was only used to ease water solubility, whereas in my experiments, DMF replaced the aqueous solution, becoming the reaction intermediate, unlike in this methodology.

Let see what Ohbayashi et al (US 6,613,564) teaches us in EXAMPLES

Example 1 Preparation of a complex of enzyme and carrier
"Then, thiol group-conjugated polylysine was prepared as follows. 6 mg of S-acetylmercaptosuccinic anhydride dissolved in 20 .mu.l of DMF was added to 5 mg of poly-L-lysine hydrobromide (manufactured by Sigma Co.; average molecular weight of 37,600 Da) dissolved in 1 ml of 0.1M sodium phosphate buffer, pH 6.5, for reaction at 30.degree. C. for 20 minutes."
"Then, thiol group-conjugated horse radish peroxidase was prepared as follows. 2.5 mg of S-acetylmercaptothioglycolic acid-N-hydroxysuccinimide ester (SATA) dissolved in 0.5 ml of DMF was added to 100 mg of horse radish peroxidase dissolved in 2.5 ml of 0.1M sodium phosphate buffer, pH 7.5, for reaction at ambient temperature for 30 minutes."

Example 5 Preparation 2 of a complex of enzyme, primary antibody and carrier
"The thiol group-conjugated anti-CD34 monoclonal antibody (manufactured by Nichirei Corp.) was prepared as follows. 0.1 mg of SATA dissolved in 50 .mu.l of DMF was added to 5 mg of anti-CD34 monoclonal antibody dissolved in 1 ml of PBS, for reaction at ambient temperature for 30 minutes."

Example 6 Preparation of a complex of enzyme and streptavidin
"Thiol group-conjugated streptavidin was prepared as follows. 0.25 mg of SATA dissolved in 250 .mu.l of DMF was added to 25 mg of streptavidin dissolved in 2.5 ml of 0.1 M sodium phosphate buffer, pH 7.5, for reaction at ambient temperature for 30 minutes."

This example is the same as the previous—the reaction was not performed in DMF, but was instead dissolved in PBS, an aqueous intermediate.

Let see what Siiman et al (US 5,639,620) teaches us in EXAMPLES

I completely agree with what Siimans teaches regarding Traut's reagent which will produce non-protected sulfur groups. This type of reactant is only produced when it can be quickly used in a following step as it is unstable. However, Traut's reagent is not my main idea. The importance of my idea lies in the creation of a stable, protected sulfur group. This results in storable, mass-producible beads in a non-aqueous solution. Thus, the over lap with Siimans, in terms of Traut's reagent is not central to my idea—without the use of Traut's reagent in my experiments, my method will still stand.

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Let see what Armstrong et al (US 5,964,996) teaches us in EXAMPLES

EXAMPLE 1
This example illustrates making a stationary phase of macrocyclic antibiotics in accordance with the present invention.
In order to make a stationary phase, 1.0 g of the macrocyclic antibiotic was dried in vacuo over P.sub.2 O.sub.5 at 100.degree. C. for four hours. Dried macrocyclic antibiotic was then dissolved (using a stirring bar) with 100 ml of anhydrous N,N-dimethyl formamide (DMF) in a 500 ml, three-neck round bottom flask. The reaction was blanketed with dry N.sub.2 gas. Dry N.sub.2 gas was introduced through one neck and initially was allowed to sweep through the apparatus and escaped through the second neck which also was fitted with a thermometer using a standard two neck adapter. The third neck of the round bottom flask was equipped with a dropping funnel which had a pressure equalizing side tube. The flask was heated using a heating mantle. When the temperature of the solution reached 90-95.degree. C., 520 .mu.l of 3-isocyanatopropyltriethoxysilane which was dissolved in 20 ml of DMF was added dropwise (at the rate of 10-15 drops/min.) while stirring the flask. After adding the reagent, the reaction was stirred for 10 hours. These steps produced a macrocyclic antibiotic-bonded-to-the-organosilane. Next, 3.5 g of silica gel (spherical, 5.mu., 100 .ANG. pore size) was dried in vacuo at 100.degree. C. over P.sub.2 O.sub.5 for four hours. The dried silica gel was then added to the DMF solution of macrocyclic antibiotic-bonded-to-the-organosilane and stirred and heated to 105.degree. C. and allowed to react for 20-24 hours. The mixture was then allowed to cool to room temperature, filtered and washed with DMF, methanol, toluene, methanol, water and methanol.

This method teaches use of DMF, but in a reaction that is not as easy or efficient as the one described in my protocol. This reaction uses difficult to control conditions such as temperatures of 100 degrees C. The reaction also takes 10+ hours to complete. This is highly inefficient and unsuitable for operation. The best industrial chemical reactions need to be carried out in easily maintained conditions, such as room temperature. Thus, my method is more suitable for industrial organic reactions in that it is not only able to be carried out under room condition, it can also produce a high yield of products.

Let see what Hansen et al (US 6,663,861) EXAMPLES

The methods taught by Hansen apply to a strictly, theoretically biological situation. Being a biologically based teaching, it still teaches the use of aqueous intermediates. It does not incorporate the aprotic intermediates that are utilized to perform the methodology described in my patent. Thus, it does not apply to industrial purposes like my patent would and it does not provide any teachings regarding the use of non-aqueous intermediates. Thus, Hansen's teachings could not possibly lead to my invention. My method and Hansen's teachings are different aspects of science, which means Hansen's teachings can not obviously lead to my methodology.

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Let see what Molna-Klmber et al (US Patent Application Publication 2002/0151088A1) EXAMPLES

Molna-Klmber's publication teaches regarding rapamycin. This is only a peripherally mentioned subject in my patent and thus does not challenge the main idea of my methodology in question. The invention in my patent is the creation of small beads. We only use rapamycin as an example of the ability and utility of the beads we create. The use of the beads can also be applied to objects larger than rapamycin. My main idea is the creation of these stable beads. Rapamycin was only an example and we are not limited to such.

3. Conclusion of Why My Patent Is Still Unique And Non-obvious

It is clear that there is one very simple but vital difference between my work and all of the prior articles. That point is my use of a non – aqueous (aprotic) solvent, specifically DMF or DMSO in my system.

You point out correctly that the starting materials and some of the products involved in my experiments have been described by previous inventors. However, I assert that the starting materials are relatively unstable in water. Specifically, our acetylated (protected) thiol in particular cannot be isolated in good yield and useful condition from a water-based reaction mixture. The prior art, which you cited, does not describe the recovery of the intermediate (protected) thiol from the reaction mixture. Instead, it is reacted immediately with the ligand without recovery of the intermediate to avoid loss by reaction with water (hydrolysis).

My use of an aprotic solvent in this system improves yield by preventing hydrolysis of starting materials (beyond the loss of material. The hydrolytic products complicate subsequent recovery of the desired product) and by protecting the desired product (Protected thiol), which is very useful for industrial purposes.

Again, the importance of my patent lies in the new methods (use of non-aqueous solvent) and results (high quantities of stable beads for industrial use) of my experiments over the general concept of the experiments.

I would now like to refute the arguments presented in the non-final rejection in the order they were presented to me. You state that Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Abrams in view of Ohbayashi because "It would have been obvious to one of ordinary skill in the art to use the SATA dissolved in DMF taught by Ohbayashi as an alternative linker in the method of Abrams to link the solid phase to the ligand since both references suggest using linkers that contain a sulfhydryl group." However, as discussed above, neither Abrams nor Ohbayashi taught this method dissolved in DMF. If you refer to the above cited paragraphs, both Abrams and Ohbayashi's experiments used DMF to enhance solubility of the reactant to enable a reaction that took place in a phosphate buffer. Thus, the basis of the argument is moot—the methods do not teach the use of SATA dissolved in DMF—SATA is dissolved in phosphate buffer, aided by DMF. In my method, DMF is actually the reaction intermediate and there are no other solutions involved at all.

Moving on, however, you state that Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Abrams in view of Ohbayashi in view of Siiman et al. because "It would have been obvious to one of ordinary skills in the art to use magnetic particles as a solid phase as taught by Siiman in the method of Abrams and Ohbayashi."

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Overlooking the above statements regarding the irrelevance of Abrams and Ohbayashi's experiments, I repeat from above that Siiman's methodology teaches to the use of magnetic particles as a solid phase using Traut's reagent. This, again, produces non-protected sulfur groups, leading to an unstable product. In comparison, my methodology produces protected sulfur groups, leading to a stable product that can be industrialized, shipped, and utilized to benefit scientific development worldwide.

Next, you state that Claim 12 is rejected as being unpatentable over Abrams in view of Ohbayashi in further view of Armstrong. We have discussed Abrams and Ohbayashi above. Armstrong, though uses DMF, requires that his reaction be carried out at a high temperature. After, he requires a complex procedure to wash the reactants using DMF, methanol, toluene, methanol, water and methanol. My method is carried out in room temperature and is washed by only DMF. In addition, my methodology is superior to that of Armstrong's, as I teach the reaction in room temperature, not the 100 degrees C that Armstrong teaches, which is difficult to maintain for highly efficient industrial results. Thus, Armstrong's patent does not teach a method that obviously leads to mine.

Following, you state that Claim 13 is unpatentable over Abrams in view of Ohbayashi, further in view of Molna-Kimber. Abrams and Ohbayashi have been discussed above. As to Molna-Kimber, I have stated above that Rapamycin is not central to my idea—it is merely an example of the capabilities of the beads created by my methodology. The beads are capable of binding to a variety of different surfaces that are not rapamycin. My main focus is the creation of these highly stable beads in a non-aqueous solution, not what the beads are capable of binding. Thus, what Molna-Kimber teaches is not central to my idea.

Lastly, you state that Claims 14 and 18 are rejected as being unpatentable over Abrams in view of Ohbayashi and further in view of Hansen et al. Again, Abrams and Ohbayashi have been discussed above. Hansen, continuing from the above stated point, teaches a purely biological method, all of which takes place in aqueous solution. Since my patent takes place in aprotic intermediate without any aqueous solution, Hansen's method is unrelated to mine and thus cannot obviously lead to my methodology.

However, since all of these subsequent claims are based on the methods of Abrams in view of Ohbayashi and their teaching of SATA in DMF. I have already proven that their methods do NOT teach that SATA is reacted in DMF at all. These teachings use DMF to increase the solubility of SATA in an aqueous solution—DMF is not the reaction intermediate, and so the rest of the further in view rejections are moot.

As proven above, my patent differs from the other arts on at least two different points. First, it teaches the use of DMF as a solvent in which the reaction can take place. Second, it produces a high yield of product able to be used commercially for the advance of scientific research. Also, the importance of my patent lies in the methodology of getting the product—and not the general idea. This methodology is unique as it combines the chemical aspects of the reaction with a set of biologically feasible conditions to produce organic solutions in an efficient and productive way. Thus, because my methodology bridges the two sciences, it is not obvious from any of these other patents—if it was, there would not be so many patents trying to do the same thing I am in much less efficient and easy ways. For example, Armstrong, et al would not have used 100 degree C conditions to carry out their reactions if it was obvious to them how to do the procedure at room temperature. My method serves as a revolution in the scientific

industry. This patent joins together the separate fields of biochemistry, organic chemistry, among others, allowing for different mediums of experiment. This patent does not focus on making reactants more soluble, but instead erases the question of solubility completely by offering new, non-aqueous intermediates that allows for reactions to cross the separate disciplines. Thus, my patent is truly a new concept that will allow the mass production of these beads for scientific research worldwide.

Sincerely,

Qing Wang

Qing Wang
95 Knickerbocker Road
Plainview, NY 11803
Tel/Fax: 1-516-390-9304
Email:qbwang888@yahoo.com

SIGNED AND ATTESTED TO MY PRESENCE THIS 20TH DAY OF JUNE 2006 AT PLAINVIEW, NEW YORK

JOSEPH LEAVY
Notary Public - State of New York
NO. 01LE6136860
Qualified in Nassau County
My Commission Expires 11/14/08

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